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PATENT APPLICATION



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

CHRISTINE NICOL, ET AL.

Application No.: 09/806,915

Filed: November 13, 2001

For: ANIMAL STEREOTYPY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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Examiner: Blessing M. Fubara

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Art Unit: 1618

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Patricia Harris, declare and say that:

1. I am currently Director of Equine Science at Effem Equine Ltd and have been in this position since 2003. I was awarded an Adjunct Professor of Equine Studies at Virginia Polytechnic Institute and State University in 2000. I have been Senior equine nutritionist at WALTHAM Centre for Pet Nutrition since 1995. In 1988 I became Head of the Clinical Chemistry and Haematology Laboratories at the Animal Health Trust, Newmarket, and of my own Metabolic Lameness Research Group.

2. I graduated from Cambridge University with an Honours Degree in 1980, qualified as a Veterinary Surgeon (as a Member of the Royal College of Veterinary Surgeons) from Cambridge Veterinary School in 1983, and in 1989 I was awarded a Doctor of Philosophy by Cambridge University for my thesis entitled "Aspects of the Equine Rhabdomyolysis Syndrome".

BEST AVAILABLE COPY

3. I am one of the named inventors of the above-identified United States Patent Application.

4. I am aware that Claims 1, 2, 7-18, 22, 23, 28-30 and 34 are rejected under 35 U.S.C. § 103(a) over Winskill *et al.*, Animal Behavior Science 48:25-35 (1996) in view of Johnson *et al.*, Equine Veterinary Journal 30(2): 139-143 (1998), further in view of Pagan, Australian Equine Veterinarian 16(4): 159-161 (1998). I am also aware that Claims 24 and 25 are rejected under § 103(a) over Johnson *et al.*, and Winskill *et al.*, in view of Pagan.

5. In order to address these rejections, I believe that the following information should be considered by the Examiner: (i) differences between the hindgut and stomach of the horse; (ii) evidence against oral use of sodium carbonate and sodium bicarbonate to reduce hindgut acidity; and (iii) why I believe that virginiamycin would not be administered as a stomach antacid.

Physiological and Gastrointestinal Differences Between the Hindgut and Stomach of the Horse

6. I believe that identification of a link between hindgut acidity and stereotypy in the horse does not mean that there is also necessarily a link between stomach acidity and stereotypy. Stomach and hindgut pH are not directly dependent on each other, and different agents or modes of administration are required to increase hindgut pH compared to those required to increase stomach pH.

7. The hindgut consists of the colon and the caecum. The volume of fluid in the digestive system changes significantly from the stomach to the hindgut. The attached Figure and Table from J. Kohnke (1998, "Feeding and Nutrition of Horses") report for example that there are 7.5-15 litres in the stomach, 40-50 litres in the small intestine, 25-30 litres in the caecum, 50-60 litres in the large colon, and 18-19 litres in the small colon.

8. The pH of the digestive system changes from acidic in the stomach, to alkaline in the small intestine, to neutral/acidic in the hindgut (Argenzio et al (1974) Am J Physiol 226, page 1048).

9. Acidity in the hindgut has a different chemical basis to stomach acidity. Abnormal acidity in the hindgut is typically caused by rapid bacterial fermentation of starch, sugar, or other carbohydrate, which leads in particular to the accumulation of lactic acid (WO 96/20709, page 1, lines 23-29, and page 5, lines 7-9). In my understanding the primary cause of stomach acidity is secretion of hydrochloric acid into the stomach.

Evidence Against Oral Use of Sodium Carbonate and Sodium Bicarbonate to Reduce Hindgut Acidity in the Horse

10. I am aware of the following evidence against the oral use of sodium bicarbonate or sodium carbonate to cause a reduction in hindgut acidity:

- a. Deuel et al. (Some Physiological Effects of Sodium Bicarbonate in Diets of Yearling Horses, Proceedings of the 7th Equine Nutrition and Physiology Symposia, Virginia, USA 1981) describes a study of the physiological effects of adding 1% sodium bicarbonate to growth diets for yearling Quarter Horses (copy attached). It is reported that feed pH was negatively correlated with fecal pH. In the Discussion on page 21 it is stated that "it has been observed that the pH of terminal colon digesta is similar to that of cecal contents ... the reduced pH of colon digesta in this study may have been associated with a reduced cecal pH". Consequently, on the basis of this study I expect that long term oral administration of 1% sodium bicarbonate may increase, rather than decrease hindgut acidity;
- b. If administered orally, sodium carbonate and sodium bicarbonate are expected to be neutralized by acid in the stomach. Rowe et al. International Horse Industry Symposium, RIRDC, 2001, left page, point 4, states that: "Buffers such as sodium bicarbonate are unlikely to reach the hindgut as the acidic conditions in the stomach convert all bicarbonate to carbon dioxide and water" (copy attached);
- c. There is a change in pH normally along the digestive system from acidic in the stomach, to alkaline in the small intestine, to neutral/acidic in the hindgut (see above);

- d. There are dramatic changes in fluid volume as food passes from the stomach to the hindgut (see above), and it takes several days for processed food to reach the rectum.

11. I believe that orally administering in particular high doses of sodium carbonate or sodium bicarbonate would alter the dietary acid/base balance of the diet and have effects on several blood parameters, including in particular the pH of the blood. This may not benefit the animal in the long term.

12. In addition, high doses of sodium carbonate may cause gastric irritation, and as far as I am aware, sodium carbonate is not administered orally to horses.

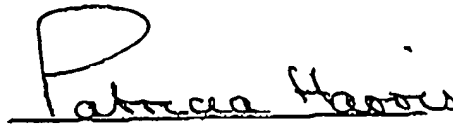
13. Oral administration of 0.5-1 g/kg body weight sodium bicarbonate has been shown to cause significant metabolic alkalosis. In some states of America I believe that the addition of sodium bicarbonate beyond a certain amount is banned in horse racing because this is thought to have the potential to affect performance.

Virginiamycin Would Not Be Administered as a Stomach Antacid

14. Virginiamycin is a streptogramin antibiotic that is specifically active against certain bacteria that ferment carbohydrate to produce lactic acid primarily in the hindgut. The primary cause of acidity in the stomach is secretion of hydrochloric acid. Consequently, if administration of virginiamycin has any significant effect on gastrointestinal pH, I expect that this would be against hindgut acidity, rather than stomach acidity. It is also banned in Europe for use in horses unless under special license for a named client.

15. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Subscribed this 6th day of October, 2006.

A handwritten signature in cursive script, appearing to read "Patricia Harris", written over a horizontal line.

Patricia Harris